3D Printing in the Catalysts of Batch and Flow Reactions

Dial-a-Molecule
Annual Meeting 2017

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3D Printing Research in the Group

MOBILE SPECTROMETER

EQUIPMENT

FLOW REACTORS

PERSONALISED MEDICINE & 4D PRINTING

SELF ASSEMBLING DEVICES

CATALYTIC REACTORS
3D Printing Process

FDM Printing
- Filament
- Motor
- Heating element
- Small Nozzle
- Solid object Produced
- Arm to lower platform
  For next layer addition

SLA Printing
- Arm to raise and lower platform
- Platform support
- Solid object Produced
- Tray to hold photopolymer
- UV transparent window
- Laser Source
  Laser beam
3D Printing Process

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**Fused Deposition Modelling (FDM) Printers**

**Stereolithography (SLA) Printers**
Total of 17 3D Printers

- Makerbot Mini
- Makerbot Mini+
- Ultimaker 2 and 3
- Makerbot Replicator 2X
- Miicraft
- FormLabs Form 1+
- FormLabs Form 2
- 3Drag

Stereolithography (SLA) Printers

Fused Deposition Modelling (FDM) Printers
3D Printing Chemistry Targets

Complex Chemistry

Heterocycle Formation

Flow / Batch Chemistry

Scale-up synthesis

Reproducible

Catalysis

Reusable technology

Erythratin

Clausenamide

γ Lycorane

Moxifloxacin

Erlotinib

Quinoxaline core
Develop reactors to take the place of the glass column reactor
Flow Chemistry - 3D Printing for prototyping/ reactions

Design based on long contact time with the heated element as shown

Unable to be produced using conventional technology

Prototype shown is in PLA

Printed at 100% infill, 9 shells

100 Micron accuracy
Flow Chemistry - 3D Printing for prototyping/ reactions

Reactor printed in polypropylene

Total weight = 21 g
Internal volume = 1.6 mL

Print time 6 hours

Material flow 110%

Capable of being heated to 150 C

Cost per reactor = £0.56

glass reactor column = £180
3D Printing – $S_N$Ar

\[
\begin{align*}
\text{DMF, } R\text{-NH}_2, \text{ DIPEA} \\
150 ^\circ \text{C}, 0.16 \text{ mL/min}
\end{align*}
\]

1a, b

0.25 mL/min, DIPEA (2eq), DMF

0.16 mL/min, DMF

\[\text{H}_2\text{N-} \]

2

3a : 66% conversion
3b : 100% conversion

a R=H; b R=CO$_2$Me
Yields 40-70%
Gram scales

Yields 50-80%

Single Diastereisomer

Flow Chemistry - 3D Printing – extension to Hydrogenation
3D Printing Catalysis in Batch Chemistry

Concept of catalytically active stirrer beads incorporating range of catalysts using FDM Printing
3D Printing Catalysis in Batch Chemistry

Concept of catalytically active stirrer beads incorporating range of catalysts using 3D Printing
FDM Printing

Catalysis via Hot Melt Extrusion
FDM Printing
3D Printing Catalysis in Batch Chemistry - Incorporation of DMAP into Polypropylene using FDM Printing

Yields: 50-80%

Bruno Sil, Bhaven Patel
Reactor Design crucial
FDM Printing uses Polypropylene and PVDF as inert polymers

Incorporation of catalysts
Extension to SLA would increase resolution and utility - 25 micron – Problem of Solvent Resistance
Stereolitography (SLA) Printing gives greater access to complex structures

Challenge of solvent resistance

Standard Resins

Solvent resistant formulation

Matthew Penny
Solvent Swelling

- H2O
- EtOH
- MeOH
- IPA
- Et2O
- THF
- Dioxane
- Acetone
- EtOAc
- MeCN
- DMF
- PhMe
- Hex
- DCM
- CHCl3
- DCE

Matthew Penny
Swelling after 2 weeks

Matthew Penny
Chemically Resistant Photopolymer

**Resistance in Refluxing solvent**

- PhMe
- THF
- DCE

**Chemical resistance**

- Et3N
- AcOH
- 6M HCl

Matthew Penny
• Sterolithography (SLA) printing
• Shape designed to maximise surface area and solvent mixing
• Catalyst loading between 5-10% (w/v)
• Resistant to nearly all solvents
Redesigned for a range of reaction sizes:

- Microwave
- Radleys Carousel
- Round Bottom Flask
- Larger Batch Scale
Efficient Mixing of Reactions

Increased Vortex and mixing of solution

Normal Stirrer 3DS Stirrer
Catalytic Stirrer Beads – Reactions

Reaction Classes

Lewis Acid Catalysis
Copper Catalysis
Palladium Catalysis
Base Catalysis

Mannich
Click Chemistry
Suzuki

Hantzsch
Chan Lam
Sonogashira

Heterocycle Formation
Heck

Amide Formation
Acylation
### Catalytic Stirrer Beads - pTsOH

#### Mannich Reaction

![Mannich Reaction](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% pTsOH impregnated stirrer bar</td>
<td>84</td>
</tr>
<tr>
<td>pTsOH impregnated stirrer bar (2&lt;sup&gt;nd&lt;/sup&gt; use)</td>
<td>81</td>
</tr>
<tr>
<td>TsOH</td>
<td>84</td>
</tr>
<tr>
<td>No catalyst</td>
<td>20</td>
</tr>
</tbody>
</table>

Catalyst: pTsOH

Conditions: H<sub>2</sub>O, 20 °C, 24 hr
Catalytic Stirrer Beads - pTsOH

Mannich Reaction

Reuse of pTsOH Catalytic Stirrer Beads

1st 2nd 3rd 4th 5th

Matthew Penny
Mannich Reaction

No reaction with stirrer or free pTsOH

52% (24 h)
47%
22% (20 h)
0% (water)

65% (3 h)
17% (22 h)

55% product rapidly degraded

91%

43%
Hantzch Synthesis

3D Synthesis Catalytic Stirrer Beads

\[
\text{OH} \quad \text{NH}_3 \quad \text{OH} \\
\text{O} \quad \text{O} \quad \text{X} \quad \text{R} \quad \text{O} \quad \text{Y} \\
\text{O} \quad \text{R} \quad \text{O} \quad \text{Y} \\
\text{p-TsOH cat., EtOH} \quad 5.5 \text{ h}
\]

Chemical structures and their yields:

- 70% yield
- 65% yield
- 73% yield
- 63% yield
- 55% yield
- 65% yield
- 73% yield
- 49% yield
- 76% yield
- 83% yield
- 66% yield
- 51% yield
- 75% yield
- 99% yield
- 50% yield
- 73% yield
- 62% yield
- 63% yield

Zenobia Rao
### 3DSynthesis Catalytic Stirrer Beads

**Heterocycle Formation**

![Chemical Reaction Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D Stirrer Bead + No Catalyst</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Normal Stirrer + Powdered Catalyst</td>
<td>2.5</td>
<td>60</td>
</tr>
<tr>
<td>3D Stirrer Bead + Powdered Catalyst</td>
<td>2.5</td>
<td>70</td>
</tr>
<tr>
<td>Catalyst Impregnated Stirrer Bead</td>
<td>5</td>
<td>86</td>
</tr>
</tbody>
</table>

Rumintha Thavarajah
### Heterocycle Formation

**Equation:**

\[
\text{Catalyst} \quad \text{Yield (\%)}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yb(OTf)\text{\textsubscript{3}}</th>
<th>CuOTf</th>
<th>Y(OTf)\text{\textsubscript{3}}</th>
<th>In(OTf)\text{\textsubscript{3}}</th>
<th>Zn(OTf)\text{\textsubscript{2}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Stirrer + Powdered Catalyst</td>
<td>61</td>
<td>36</td>
<td>25</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>3D Stirrer Bead + Powdered Catalyst</td>
<td>64</td>
<td>54</td>
<td>33</td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td>Catalyst impregnated 3D Stirrer Bead</td>
<td>78</td>
<td>76</td>
<td>37</td>
<td>34</td>
<td>65</td>
</tr>
</tbody>
</table>

Ruminthha Thavarajah
Click Chemistry

3D Synthesis Catalytic Stirrer Beads

Reuse of Copper Click Catalytic Stirrer Beads

Moussa Sehailia
Click Chemistry

3DSynthesis Catalytic Stirrer Beads

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{N}_3 & \quad \text{Cu(I) or Cu(II)} \\
\text{3DStirrer} & \quad \text{R}
\end{align*}
\]

Moussa Sehailia
Palladium Chemistry

Suzuki coupling

0.25% Loading of Tetrakis Pd(PPh₃)₄ Per bead

Stable at room temperature

Reusable up to 5 times

Average 99%

Reuse of Pd Tetrakis Catalytic Stirrer Beads

Zenobia Rao
3DSynthesis Catalytic Stirrer Beads

Palladium Chemistry

**Chemical Reaction:**

```
PhB(OH)
```

```
PhCO
```

**Reagents:**

- EtOH, H₂O, Na₂CO₃
- 120 °C

**Yield:** 99%

**Product:****

```
PhCO
```

**Reagents:**

- EtOH, H₂O
- Na₂CO₃
- 120 °C

**Yield:** 99%

---

**Additional Products:**

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>85%</td>
</tr>
<tr>
<td>F</td>
<td>99%</td>
</tr>
<tr>
<td>NO₂</td>
<td>94%</td>
</tr>
<tr>
<td>CF₃</td>
<td>96%</td>
</tr>
<tr>
<td>O</td>
<td>98%</td>
</tr>
<tr>
<td>O</td>
<td>93%</td>
</tr>
<tr>
<td>O</td>
<td>60%</td>
</tr>
<tr>
<td>H</td>
<td>99%</td>
</tr>
<tr>
<td>Cl</td>
<td>94%</td>
</tr>
<tr>
<td>O</td>
<td>87%</td>
</tr>
<tr>
<td>NO₂</td>
<td>73%</td>
</tr>
<tr>
<td>NO₂</td>
<td>81%</td>
</tr>
<tr>
<td>O</td>
<td>97%</td>
</tr>
</tbody>
</table>
Microwave acceleration/ enhancement

Suzuki coupling

Bromides – lower Yielding

Microwave – reduction in time – 12 hours to 20-30 minutes

73%  85%  77%  73%
Microwave Reaction

Combination of Pd and Copper catalysts in the same bead

2 hours 50-80% yields
Additional Reactions

**Chan Lam**

- **Ester Formation**
  
  \[ \text{PhOH} + \text{CO}_2 \rightarrow \text{PhCO}_2 \text{H} \]

  
  **Catalyst:** DMAP Stirrer Bead

**Amide Formation**

- **Amide Formation**
  
  \[ \text{PhCO}_2 \text{H} + \text{PhNH}_2 \rightarrow \text{PhCONHPh} \]

  
  **Catalyst:** TBD Stirrer Bead
Flow Chemistry – Reactor Types

Reactor Design

Ability to Print any shape and reactor size

Incorporation of PEEK fittings/screw threads

Resistant to solvent
Photochemical Flow Reactors

Extension into Flow Chemistry

Chemically Inert Polymer

Flow Photochemistry via attachment to glass top over reactor bed – DCE as solvent in photodecarboxylation
**Catalytic Flow Reactors**

Single Split-wide reactor

Actinic bulb – scale up via additional Reactors

Catalytic reactors – containing Zinc triflate

DrySyn Flow Reactors

- Flow Photochemistry
- Catalytic Flow Chemistry
- Stable up to 20 bar
- Readily configurable
- Built and designed with peek fitting threads
- Can be easily linked
- Modified flow path

Zenobia Rao
DrySyn Flow Reactors for Catalysis in Flow using Impregnated Catalysts
Flow Photochemistry

- Suitable with DMF - 16 bar pressure
- Actinic bulb with cooling
- Flow rates 0.1 - 0.05mL/min
- Yields ~80%

\[
\text{MeOC}_6\text{H}_4\text{NPh}_2 (2 \text{ eq.}),
\]

Cat. (0.01 eq), DMF
Great potential in the efficient catalysis of a wide array of reaction classes.

Low cost and applicable to both batch and continuous flow
Acknowledgements

Group

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